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SHORT TAKE

Telomere length behaves as biomarker of somatic redundancy rather than biological age

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Summary

Biomarkers of aging are essential to predict mortality and aging-related diseases. Paradoxically, age itself imposes a limitation on the use of known biomarkers of aging because their associations with mortality generally diminish with age. How this pattern arises is, however, not understood. With meta-analysis we show that human leucocyte telomere length (TL) predicts mortality, and that this mortality association diminishes with age, as found for other biomarkers of aging. Subsequently, we demonstrate with simulation models that this observation cannot be reconciled with the popular hypothesis that TL is proportional to biological age. Using the reliability theory of aging, we instead propose that TL is a biomarker of somatic redundancy, the body's capacity to absorb damage, which fits the observed pattern well. We discuss to what extent diminishing redundancy with age may also explain the observed diminishing mortality modulation with age of other biomarkers of aging. Considering diminishing somatic redundancy as the causal agent of aging may critically advance our understanding of the aging process, and improve predictions of life expectancy and vulnerability to aging-related diseases.

Key words: blood pressure; body mass index; cholesterol; Gompertz; mechanisms of aging; senescence; Weibull.

Biomarkers are used to assess health, risk of aging-related diseases and remaining lifespan. However, the association with mortality of well-studied biomarkers, such as blood pressure (BP), cholesterol (CHOL) and body mass index (BMI) diminishes with age (Prospective Studies Collaboration, 2002, 2007, 2009), indicating that they provide less information in old compared with young subjects. How this pattern arises is not yet understood, despite its relevance for understanding and predicting aging. We investigated this phenomenon using data on telomere length (TL). Telomeres are terminal DNA–protein complexes that protect chromosomes, but shorten with age (Armanios & Blackburn, 2012; and references therein). TL is a candidate biomarker of aging, but studies linking TL and mortality have yielded inconsistent results. Weak relationships were found in the oldest cohorts, suggesting that the association of TL and mortality diminishes with age (Martin-Ruiz *et al.*, 2005; Bischoff *et al.*, 2006). However, whether sampling age explains the observed study heterogeneity has not been quantitatively tested. We carried out meta-analyses to: (i) test whether TL predicts mortality and (ii) test whether the association of TL and mortality diminishes with age.

Literature search yielded 16 eligible studies (SI–I.A) comprising 10 157 individuals, with an average follow-up of 7.9 years during which 36% died. Effect sizes were expressed as hazard ratios (HR), the change in mortality risk associated with a decrease of 1 kbp in TL. Across studies, the natural log (ln) of the HR of TL was larger than zero (lnHR = 0.112; P = 0.007), indicating that longer TL was associated with lower mortality risk (SI–I). As hypothesized, lnHR of TL diminished with sampling age (Fig. 1; slope for ln age = −0.822; 95% CI −1.556, −0.088; P = 0.028), from lnHR = 0.29 at age 63 to a negligible level (lnHR < 0.05) at age ≥85. We conclude therefore that TL predicts mortality, but this association diminishes with age.

This pattern of diminishing mortality modulation (DMM; Fig. 1) raises fundamental questions about the relationship between age, TL and mortality. We tested two different models of this relationship using simulation models. Our first model was based on the popular perception of TL as indicator of biological age (e.g. Aviv, 2002) in the sense that, for example, 70-year-old individuals with a TL of the average 60-year-old individual will experience the mortality risk of someone 10 years younger. More complex links between a biomarker and biological age can be envisaged, but in our perception this is the most common and simplest way that a biomarker is interpreted as indicator of biological age. We simulated mortality data using the Weibull distribution, and subsequently analysed these data on the association of TL, age and mortality using meta-regression analysis (see SI–II and SI–III.A for details on general simulation procedures and the biological age model respectively). HR of TL declined with subject age, but in the best fitting simulation results the slope was only ~10% of the observed slope (slope = −0.082 vs. −0.822; Fig. 1). Repeating this analysis using the Gompertz distribution yielded the same result (SI–III.B; Fig. S2).

Our second model assumed TL to be a measure of somatic redundancy. It has been hypothesized that organisms consist of redundancy elements that can functionally replace each other, allowing for damage to accumulate until the last element fails, causing death. The redundancy elements themselves are assumed to be nonaging in that they have a constant failure rate over time. The resulting redundancy exhaustion generates mortality trajectories with age that resemble observed mortality patterns (Gavrilov & Gavrilova, 2001). Treating TL as

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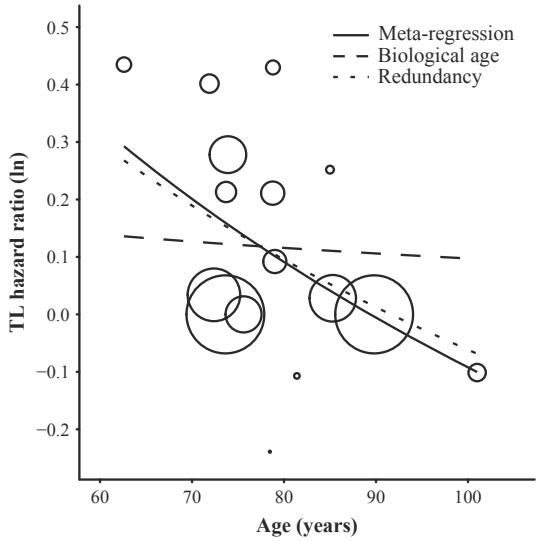

Fig. 1 Meta-regression analysis of the association between mortality predicted by telomere length (TL) and ln age (continuous line). Bubble area is proportional to weight in the analysis (1/s.e.^{2}). Dashed lines depict the simulated mortality association of TL according to biological age (long dash) and redundancy (short dash).

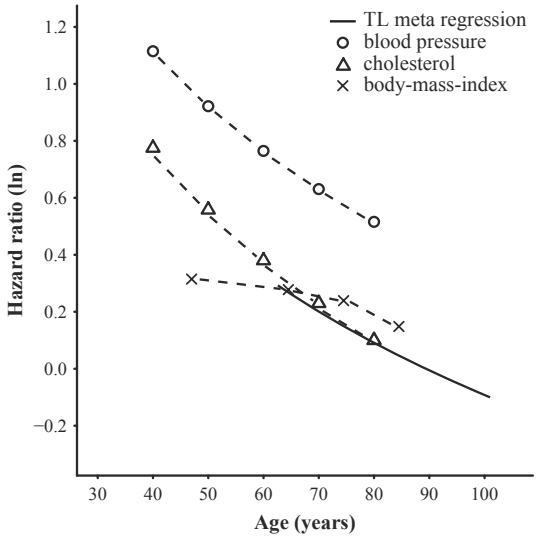

Fig. 2 DMM of BP (○), CHOL (Δ) and BMI (×). The meta-regression line of TL is shown as a reference (solid line). HR values of BP, CHOL and BMI were obtained from Prospective Studies Collaboration, 2002, 2007, 2009.

measure of redundancy is at least superficially compatible with the observation that long telomeres shorten faster than short telomeres (Grasman *et al.*, 2011; and references therein) because with more redundancy elements also more are lost per unit of time. Furthermore, this approach is compatible with the observation that telomere shortening does not influence cell performance until a threshold limit is reached inducing cell cycle arrest (reviewed in Armanios & Blackburn, 2012). Thus, although we do not suggest that TL is a direct measure of somatic redundancy, we do consider that telomeres share critical features with redundancy elements. We considered TL as index of the number of redundancy elements, and simulated mortality data using this model (SI–IV). HR of TL declined with subject age in the simulated data with a slope close to the observed pattern (Fig. 1; slope −0.704 vs. −0.822). The redundancy model was substantially better than the biological age model in generating data that resembled the observations (ΔAIC = 4.0; SI–II.C) and we therefore conclude that the redundancy model best describes DMM of TL with age.

The pattern of DMM with age of TL resembles the patterns reported for other biomarkers of aging (Fig. 2), confirming its generality. This resemblance raises the question whether, like TL, the DMM of BP, CHOL and BMI also results from diminishing redundancy with age. This is not obvious, given that the analogy that exists between redundancy elements and telomeres is not clear for these other biomarkers. On the other hand, we do not consider it likely that there are directly measurable redundancy 'elements' existing within a single physiological structure or system. Instead, we consider redundancy to be an abstraction comprising a multitude of aspects of physiological state that together determines the body's capacity to absorb damage. When our interpretation is correct that diminishing somatic redundancy with age is causal to the aging process, we would predict each biomarker of aging to reflect diminishing redundancy. However, whether this interpretation applies to BP, CHOL and BMI remains to be verified.

Our findings are in agreement with the assumption that diminishing redundancy is causal to aging, but DMM with age of TL could also arise if the relation between TL and mortality is nonlinear. When only a certain range of TL is associated with mortality, then TL may no longer predict mortality in the surviving subjects with TL outside this range. Because we found no evidence for nonlinearity within the studies included in our meta-analysis, we consider it realistic to assume that mortality risk is linearly related with TL.

We recognize, however, that our evidence for diminishing redundancy as causal agent of aging is circumstantial, and it is important to note therefore that the redundancy model yields an additional prediction regarding biomarkers of aging. Due to the reduction in redundancy variance between individuals with age, redundancy element failure rate becomes increasingly important in predicting mortality. Verifying whether this prediction is supported by data would thus be a key test of the redundancy model of aging, and such a test may in particular be feasible using telomeres because for this biomarker the rate of telomere attrition can be used as proxy for element failure rate. The data for a comprehensive test of this prediction using TL are unfortunately not yet available, but we note that promising preliminary support comes from one recent study showing that at old age telomere shortening more accurately predicted mortality than TL itself (Epel *et al.*, 2009), in accordance with the redundancy model of aging.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Data S1 SI I–IV.